EXHIBIT 3

weeks and it is preferable to err on the longer interval than a shorter one. The interval between the second and third injections should be even longer, with at least five or six months in between. Again, it is better to err on the longer interval. This schedule makes the original fourth booster dose in the second year of life no longer necessary.

If a potent adjuvant DTP vaccine is used with the intervals between the first and second doses as stated, the interval between the second and third can be as long as 9 to 12 months with an adequate response, but it is always preferable to keep to the recommended schedule ('Immunisation Against Infectious Diseases', issued by the Department of Health and Social Security, Alexander Fleming House, Elephant and Castle, London SE1 6BY. July 1972).

PROFESSOR J. A. DUDGEON, M.C., T.D., M.D., M.R.C.P.

Black Hairy Tongue

QUERY (from a reader in Malta).—I should be grateful if you could tell me whether there are any new findings on the cause and treatment of 'black hairy tongue'.

A married woman, aged 49 years, who had a total hysterectomy two years ago for metropathia haemorrhagica, has developed a black hairy tongue during the past nine months. The tongue is covered in black hair in the centre towards the back; she complains of a taste of mud. She shows no other signs of the menopause.

After having undergone various courses of antifungal and viramin treatment she is now very distressed about her condition.

REPLY.—Black hairy tongue may follow the use of local or systemic antibiotics or occur without obvious cause. Regular gentle brushing with a soft toothbrush may be effective in removing the hypertrophied papillae. Tomaszewski (1953) reported that antibiotic lozenges, while causing the colour of the tongue to deepen for a few days, make the hairs more easy to remove.

I am not aware of any new findings on the cause or treatment of this distressing condition.

Reference

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R. H. BALME, D.M., F.R.C.P.

Interruption of Oral Contraception

QUERY.—With regard to the contraceptive pill, at one time it was the practice that this should be discontinued for a month each year in women wishing further family. Is this now considered necessary?

REPLY.—It has never been accepted practice to advise women using oral contraceptives to stop them unless they wished to have a family, the need for contraception had ceased, or contraindications to further use of the pill had arisen. It seems that the confusion which still exists on this point arose from the fact that, when the Food and Drugs Administration of the USA first licensed oral contraceptives for clinical use they stipulated that this was to be for a period of two years. On reviewing the position at the end of that time, the licence was extended for a further two years. A second review, at the end of four years' experience, led the FDA to withdraw the time limit altogether. The accumulated experience of some 15 years of clinical use of oral contraceptives has failed to show that any advantage accrues from interrupting the use of the pill, other than for the reasons mentioned above.

G. I. M. SWYER, D.M., F.R.C.P.

Research on Anticarcinogenic Effects of Thalidomide

QUERY.—While carrying out a literature survey for my research into 'drug complex formation' it occurred to me that teratogenic drugs such as thalidomide should be of value in the treatment of cancer. As a physicist my knowledge in this field is very limited and I would appreciate the opinion of your medical experts.

REPLY.—It is well known that some teratogens exhibit tumour-inhibitory activity and may also be mutagens and/or carcinogens. It is not surprising therefore that the above question has arisen in the minds of others (Hunter, 1962; Rogerson, 1962). Workers at the Chester Beatty Research Institute (Roe and Mitchley, 1963) saw no inhibition of the growth of the transplantable Walker tumour in rats in response to thalidomide. Bach and his colleagues (1963) obtained

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F. J. C. ROE,

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negative results when they gave thalidomide to mice bearing either of two transplantable tumours, and DiPaolo (1963) found thalidomide to be ineffective against eight transplantable tumours in mice. Thalidomide may exhibit feeble carcinogenic activity (Roe and Mitchley, 1963; Roe *et al.*, 1967) but is not apparently mutagenic for Drosophila (Luers, 1962). The various laboratory findings provided no encouragement for the view that thalidomide might be of practical value in the treatment of human cancer. Furthermore, two clinical trials (Olson *et al.*, 1965; Grabstald and Golbey, 1965) involving a total of 92 cancer patients revealed no real evidence that thalidomide exhibited useful anticancer activity although the drug had significant palliative value.

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F. J. C. ROE, D.M., D.SC., F.R.C.PATH.

Behçet's Syndrome

QUERY (from a reader in Iraq).—A 30-year-old man has had repeated attacks of stomatitis, ulcerative eye lesions involving the conjunctivae and uveal tract, ulceration on the genitalia, and also pelvic ulceration, but without urethral discharge. He also has low-grade fever and joint pain. The picture suggests Behçet's syndrome. He has had these symptoms for the past 2½ years and has been given antibiotics by mouth and injection, local treatment to the eye, and Prednisone tablets. Remissions occur but the condition relapses if the dosage of drugs is reduced. I should appreciate an expert opinion.

REPLY.—The clinical features of this case are certainly consistent with Behçet's syndrome—a condition of unknown etiology for which no treatment is of proven value. Before finally accepting such a diagnosis, it would be as well to make sure that the blood count is normal, since chronic leucopenia may present in this way in association with splenomegaly in some cases and with rheumatoid arthritis in others (Felty's syndrome) or as part of systemic lupus erythematosus, and most of these conditions respond to steroids. Careful examination of the gastrointestinal tract also would be indicated to exclude ulcerative colitis or possibly Crohn's disease in this case and it should be remembered that sensitivity to drugs (especially Phenylbutazone or Sulphonamides) could produce these symptoms.

If none of these conditions is present, the diagnosis of Behçet's syndrome may be accepted. The condition does not always respond to steroids, and antibiotics are not helpful except in the treatment of definite bacterial complications such as pneumonia. The combination of long-term antibiotics and steroids would be particularly likely to lead to opportunistic infection with unusual antibiotic-resistant organisms of low virulence, especially fungi. It would be important to correct any nutritional deficiencies, especially of water-soluble vitamins or protein. Local treatment with Hydrocortisone pellets may help the mouth lesions.

In this particular patient, if there is a clear-cut remission of symptoms and improvement in signs on oral Prednisone this drug may have to be continued indefinitely. Once the remission is induced the Prednisone dosage should be reduced very gradually. If the initial dosage has had to be high, e.g. 60 mg a day, it will generally be possible to cut it by 5 mg every other day until a level of about 20 mg is reached. Thereafter an even more gradual reduction in dosage would be necessary and reductions of 1 mg in the daily dose every four days or so is suggested. In this way it may be possible to reach a low maintenance dose. A dose of less than 10 mg a day of Prednisone should not produce severe side-effects and 10 to 20 mg a day may be well tolerated provided the patient remains physically active and takes a diet with adequate protein, vitamins and calcium content. Much larger doses can be tolerated for short periods.

R. H. BALME, D.M., F.R.C.P.